A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/85 A61K48/00 C12N15/52 C12N15/53 C12N9/00
C12N9/02 C12N15/86 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A01K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GU, H. ET AL.: "Deletion of a DNA polymerase beta gene segment in T cells using cell type-specific gene targeting" SCIENCE., vol. 265, 1 July 1994 (1994-07-01), pages 103-106, XP000857325 AAAS. LANCASTER, PA., US	1-3,5,6, 13,14
Y	page 104, column 1, paragraph 2 -column 3, paragraph 2; figure 1 page 105, column 2, paragraph 3 -column 3, paragraph 2	1-9,11, 13-18, 23-25, 27,28, 36,41

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2000	13/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chambonnet, F

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 195 30 412 A (MELCHNER HARALD VON PROF DR ;GREZ MANUEL DR (DE); RUSS ANDREAS PET) 20 February 1997 (1997-02-20)	1,2,5,6, 8,14-18
Y	the whole document	1-4,7,9, 13-18, 23-25, 27,28,41

X	ANTON M ET AL: "SITE-SPECIFIC RECOMBINATION MEDIATED BY AN ADENOVIRUS VECTOR EXPRESSING THE CRE RECOMBINASE PROTEIN: A MOLECULAR SWITCH FOR CONTROL OF GENE EXPRESSION" JOURNAL OF VIROLOGY,US,THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 69, no. 8, August 1995 (1995-08), pages 4600-4606-4606, XP002011775 ISSN: 0022-538X cited in the application	1,2,5,6, 8,14
Y	page 4602, column 1, paragraph 2 -page 4605, column 2, paragraph 4	2,4,9, 11, 23-25, 27,28,36

Y	KANEGAE Y ET AL: "EFFICIENT GENE ACTIVATION IN MAMMALIAN CELLS BY USING RECOMBINANT ADENOVIRUS EXPRESSING SITE-SPECIFIC CRE RECOMBINASE" NUCLEIC ACIDS RESEARCH,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 23, no. 19, 11 October 1995 (1995-10-11), page 3816-3821 XP002011774 ISSN: 0305-1048 the whole document	1,2,5,6, 8,14

Y	WANG P ET AL: "HIGH FREQUENCY RECOMBINATION BETWEEN LOXP SITES IN HUMAN CHROMOSOMES MEDIATED BY AN ADENOVIRUS VECTOR EXPRESSING CRE RECOMBINASE" SOMATIC CELL AND MOLECULAR GENETICS,US,NEW YORK, NY, vol. 21, no. 6, 1995, page 429-441 XP000617918 the whole document	1,2,5,6, 8,11,14, 36

	-/--	

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FERNEX, C. ET AL: "Cre/loxP mediated excision of a neomycin resistance expression unit from an integrated retroviral virus increases Long Terminal Repeat-driven transcription in human hematopoietic cells" JOURNAL OF VIROLOGY., vol. 71, no. 10, October 1997 (1997-10), pages 7533-7540, XP000857099 ICAN SOCIETY FOR MICROBIOLOGY US	1,4,5
Y	the whole document	4
Y	WO 98 10086 A (UNIV PENNSYLVANIA ;PHANEUF DANIEL (US); WILSON JAMES M (US)) 12 March 1998 (1998-03-12) the whole document	1,2,5,6, 8,11,14, 36
Y	HALLAHAN, D.E. ET AL.: " Spatial and temporal control of gene therapy using ionizing radiation" NATURE MEDICINE, vol. 1, no. 8, August 1995 (1995-08), pages 786-791, XP000857200 cited in the application the whole document	1,4,11, 16, 23-25, 27,28
Y	HALLAHAN, D.E. ET AL.: "c-jun and Egr-1 participate in DNA synthesis and cell survival in response to ionzzing radiation exposure" JOURNAL OF BIOLOGICAL CHEMISTRY (MICROFILMS), vol. 270, no. 51, 22 December 1995 (1995-12-22), pages 30303-30309, XP000857098 MD US cited in the application the whole document	23,27,28
Y	ELLIOTT G ET AL: "INTERCELLULAR TRAFFICKING AND PROTEIN DELIVERY BY A HERPESVIRUS STRUCTURAL PROTEIN" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 88, 24 January 1997 (1997-01-24), page 223-233 XP002064725 ISSN: 0092-8674 the whole document	9

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Y	LAKSO, M. ET AL.: "Targeted oncogene activation by site-specific recombination in transgenic mice" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 89, July 1992 (1992-07), pages 6232-6236, XP000857321 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 cited in the application the whole document	1,2,5-7, 11,14
Y	WO 92 15694 A (SALK INST FOR BIOLOGICAL STUDI) 17 September 1992 (1992-09-17) claims 1-9,13-18,29-34,46,58,59	1,5,6, 14,41
Y	WO 97 17842 A (UNIV ROCHESTER) 22 May 1997 (1997-05-22) the whole document	1,5-7,11

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19530412 A	20-02-1997	AU 4941096 A	12-03-1997
		WO 9707223 A	27-02-1997
		EP 0845041 A	03-06-1998
		JP 11511018 T	28-09-1999
WO 9810086 A	12-03-1998	AU 4183097 A	26-03-1998
		EP 0950111 A	20-10-1999
WO 9215694 A	17-09-1992	US 5654182 A	05-08-1997
		US 5677177 A	14-10-1997
		US 5885836 A	23-03-1999
WO 9717842 A	22-05-1997	AU 1159697 A	05-06-1997
		CA 2237392 A	22-05-1997
		EP 0952767 A	03-11-1999

TENT COOPERATION TRE. /

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 December 1999 (21.12.99)	
International application No. PCT/GB99/01362	**Applicant's or agent's file reference**
International filing date (day/month/year) 17 May 1999 (17.05.99)	**Priority date** (day/month/year) 15 May 1998 (15.05.98)
Applicant MARGISON, Geoffrey, Paul et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 November 1999 (29.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JNHS		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01362	17/05/1999	15/05/1998
International Patent Classification (IPC) or national classification and IPC C12N15/85		
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/11/1999	02.05.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giebeler, K Telephone No. +49 89 2399 8546

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01362

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-66 as originally filed

Claims, No.:

1-53 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 49 and 50 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 49 and 50 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-53
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-53
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-48, 51-53
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 49 and 50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. The following documents are cited:

   D1: GU, H. ET AL.: SCIENCE., vol. 265, 1 July 1994, pages 103-106
   D2: DE 195 30 412 A
   D3: ANTON M ET AL: JOURNAL OF VIROLOGY, vol. 69, no. 8, August 1995, pages 4600-4606-4606,
   D6: FERNEX, C. ET AL: JOURNAL OF VIROLOGY., vol. 71, no. 10, October 1997, pages 7533-7540,
   D8: HALLAHAN, D.E. ET AL.: 'NATURE MEDICINE, vol. 1, no. 8, August 1995 , pages 786-791

3. The subject-matter of claims 1-53 appears to be novel over the available prior art.

   In D1, the recombination system results in the deletion of the target gene, not in its expression. In D2, the recombinase does not have the capacity to establish an operative linkage between the tk-neo gene and the pgk promoter. In D3 and D6, the recombinase gene is not under the control of a regulatory system responsive to the effect of an expression inducing influence.

4. The subject-matter of claim 1 appears to be based on an inventive step.

D8, which discloses vector material containing a tumour cell sensitizing gene (tnf-alpha) under the control of the radiation-inducible Egr-1 promoter region, appears to represent the closest prior art document.

The subject-matter of claim 1 is distinguished therefrom in that the "expression inducing influence" (e.g. radiation) results in the expression of a control gene, the expression product of which can establish continuous production of the tumour cell sensitizing gene product. Thus, a transient inducing influence results in the continuous production of the tumour sensitizing gene product.

The technical problem to be solved is seen in the provision of vector material suitable for cancer therapy having improved regulation properties.

The solution to this problem as provided by claim 1 does not appear to be obvious over the available prior art for the following reasons.
The cre/lox recombination system was well-known at the priority date of the application and had been widely used. D3, for instance, discloses a vector construct containing the luciferase gene under control of the HCMV immediate early promoter, but separated from it by an extraneous spacer sequence flanked by lox P sites, which blocks luciferase expression. Cre-mediated excision of the intervening sequence resulted in induction of luciferase expression.
However, it appears that none of the available prior art documents suggests the use of the cre recombination system in order to achieve continuous production of a desired gene product following a transient signal. Therefore, it would appear that a person skilled in the art would not have solved the problem posed by providing the subject-matter of claim 1.

Accordingly, the subject-matter of claims 2-53 also appears to involve an inventive step.

5. The subject-matter of claims 1-48 and 51-53 furthermore appears to be industrially applicable.

8 L

'ATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/01362	17/05/1999	15/05/1998
Applicant		
CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED. et al		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01362

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/85 A61K48/00 C12N15/52 C12N15/53 C12N9/00
C12N9/02 C12N15/86 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N A01K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GU, H. ET AL.: "Deletion of a DNA polymerase beta gene segment in T cells using cell type-specific gene targeting" SCIENCE., vol. 265, 1 July 1994 (1994-07-01), pages 103-106, XP000857325 AAAS. LANCASTER, PA., US	1-3,5,6, 13,14
Y	page 104, column 1, paragraph 2 -column 3, paragraph 2; figure 1 page 105, column 2, paragraph 3 -column 3, paragraph 2	1-9,11, 13-18, 23-25, 27,28, 36,41

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 2000	13/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chambonnet, F

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X Y	DE 195 30 412 A (MELCHNER HARALD VON PROF DR ;GREZ MANUEL DR (DE); RUSS ANDREAS PET) 20 February 1997 (1997-02-20) the whole document	1,2,5,6, 8,14-18 1-4,7,9, 13-18, 23-25, 27,28,41
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Y	page 4602, column 1, paragraph 2 -page 4605, column 2, paragraph 4	2,4,9, 11, 23-25, 27,28,36
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Y	WANG P ET AL: "HIGH FREQUENCY RECOMBINATION BETWEEN LOXP SITES IN HUMAN CHROMOSOMES MEDIATED BY AN ADENOVIRUS VECTOR EXPRESSING CRE RECOMBINASE" SOMATIC CELL AND MOLECULAR GENETICS,US,NEW YORK, NY, vol. 21, no. 6, 1995, page 429-441 XP000617918 the whole document	1,2,5,6, 8,11,14, 36

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Y	the whole document	4
Y	WO 98 10086 A (UNIV PENNSYLVANIA ;PHANEUF DANIEL (US); WILSON JAMES M (US)) 12 March 1998 (1998-03-12) the whole document	1,2,5,6, 8,11,14, 36
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Y	ELLIOTT G ET AL: "INTERCELLULAR TRAFFICKING AND PROTEIN DELIVERY BY A HERPESVIRUS STRUCTURAL PROTEIN" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 88, 24 January 1997 (1997-01-24), page 223-233 XP002064725 ISSN: 0092-8674 the whole document	9

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Y	LAKSO, M. ET AL.: "Targeted oncogene activation by site-specific recombination in transgenic mice" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 89, July 1992 (1992-07), pages 6232-6236, XP000857321 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 cited in the application the whole document	1,2,5-7, 11,14
Y	WO 92 15694 A (SALK INST FOR BIOLOGICAL STUDI) 17 September 1992 (1992-09-17) claims 1-9,13-18,29-34,46,58,59	1,5,6, 14,41
Y	WO 97 17842 A (UNIV ROCHESTER) 22 May 1997 (1997-05-22) the whole document	1,5-7,11

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/GB 99/01362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19530412 A	20-02-1997	AU 4941096 A	12-03-1997
		WO 9707223 A	27-02-1997
		EP 0845041 A	03-06-1998
		JP 11511018 T	28-09-1999
WO 9810086 A	12-03-1998	AU 4183097 A	26-03-1998
		EP 0950111 A	20-10-1999
WO 9215694 A	17-09-1992	US 5654182 A	05-08-1997
		US 5677177 A	14-10-1997
		US 5885836 A	23-03-1999
WO 9717842 A	22-05-1997	AU 1159697 A	05-06-1997
		CA 2237392 A	22-05-1997
		EP 0952767 A	03-11-1999

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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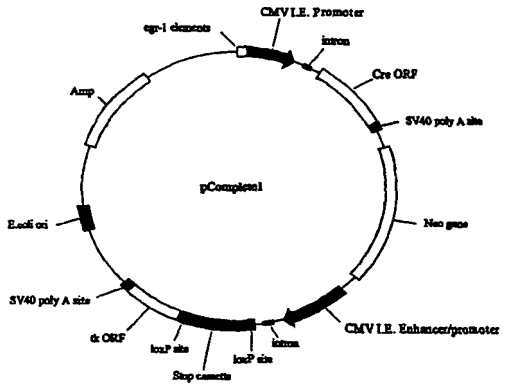

(57) Abstract

Vector material useful for antitumour therapy contains: (a) a tumour cell sensitizing gene or genes of which expression in a tumour cell yields a sensitizing gene expression product having a potential to cause tumour cells to be killed and destroyed, or to be eliminated, or otherwise to be inactivated, or to be rendered sensitive and/or vulnerable to destruction; (b) a sensitizing gene promoter; (c) at least one control gene; and (d) a control gene expression regulatory system responsive in use in a transfected cell to the effect of a predetermined exogenous or endogenous expression inducing influence, e.g. ionizing radiation, heat or a chemical inducing agent, so as to induce expression of the control gene to yield an expression product having a capacity to establish an operative linkage between the sensitizing gene promoter and the sensitizing gene or genes effective to trigger and switch on or permit continuous or permanent expression of the latter to bring about continuous production of the sensitizing gene expression product. This is preferably achieved by arranging for the control gene to encode a recombinase enzyme that acts on recombinase target sites in a Cre–loxP or Flp–frt site specific recombination system to remove an expression preventing stop cassette sequence between the sensitizing gene(s) and the promoter for the latter. In some embodiments the tumour sensitizing gene expression product will be an enzyme or other bioactive agent that can activate an inactive prodrug.

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